species election of a "specific method of modulation encompassing a specific agent", or "specific pair of agents", or a "specific method for treating a specific condition encompassing administration of a specific agent", or a "specific method of *ex vivo* modulation encompassing a specific pair of reagents".

Accordingly, although Applicants believe that a restriction under 35 U.S.C. §121 is improper given generic claim 1, a species election may be proper for searching purposes only, posing no undue burden on the Examiner. Thus, Applicants hereby elect the following: (1) the species of stimulation of a Th2-type response; (2) the subspecies of a non-soluble form of B7-2; (3) the subspecies of a stimulatory form of B7-2 attached to a solid phase support; (4) the subspecies of anti-CD3 antibody to activate a population of CD4+ T cell; (5) the subspecies of a an autoimmune disease as a condition in a subject to be ameliorated and (6) the subspecies of multiple sclerosis as the autoimmune disease.

Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 2 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner argues that,

> [C]laim 2 is indefinite for reciting "wherein the Th2-type response is stimulated" because it is not clear what is meant by stimulating an ongoing Th2-type response. If the meaning intended is that of skewing the response towards being a Th2 response or inducing a Th2 response, it is suggested that the claim be changed to recite "wherein a Th2 response is induced".

Applicants respectfully submit that the above rejection does not apply to claim 2 as amended. Claim 2 has been amended as suggested by the Examiner to recite "wherein a Th2 response is induced". Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claims 1-4 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Hathcock *et al.* [J. Exp. Med. 180: 631-40 (Aug. 1994)] in view of Linsley *et al.* [U.S. Patent 5,580,756 (Mar. 1990)], Kuchroo *et al.* [Cell 80: 707-718 (Mar. 1995)] and Janeway *et al.* [Cell 76:275-285 (Jan. 1994)].

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully solicited.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, as in the instant rejection, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Claim 1 is directed to a method for selectively modulating a Th2-type response within a population of activated CD4+ T cells by contacting the population of activated CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of

activated CD4+ T cells, such that the Th2-type response is modulated. Claim 2 is directed to a method of claim 1 in which the Th2-type response is induced by contacting the population of activated CD4+ T cells with an agent which stimulates a B7-2-induced signal. Claim 3 is directed to a method of claim 2 in which the agent which stimulates a B7-2-induced signal in the population of activated CD4+ T cells is a stimulatory form of B7-2. Claim 4 is directed to a method of claim 3 in which the stimulatory form of B7-2 is a form of B7-2 which is attached to a solid phase support.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references fail to teach or suggest the claimed methods. Applicants arguments in support of this position are set forth in the following subsections.

A. Hathcock *et al.* fail to teach or suggest different roles for B7-1 and B7-2

The Examiner relies on Hathcock *et al.* for teaching the expression, regulation and function of B7-2, and for teaching that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response. In particular, the Examiner contents that,

> [H]athcock *et al.* teach that in response to LPS or anti-IgD-dextran, murine B cells express B7-2 earlier and at higher levels than B7-1 and that such quantitative differences in the amount of B7-1 and B7-2 expressed on activated B cells may, profoundly influence their contribution to costimulatory function (Pages 634 and 638, in particular).

First, Applicants submit that Hathcock *et al.* teach the following observations which are set forth in the "Summary" section at page 631: (a) B7-1 and B7-2 can be expressed by multiple cell types, including B cells, T cells, macrophages, and dendritic cells; (b) stimulating B cells with either LPS or anti-IgD-dextran induced expression of both B7-1 and B7-2; (c) blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production; and (d) expression of B7-1 and of

B7-2 can be regulated by a variety of stimuli. Hathcock *et al.* do not teach or suggest ***modulating a Th-2 type response*** in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. In fact, there is no teaching in Hathcock *et al.* relating to the Th-1 and Th2 pathways of maturation of CD4+ T cells, nor is there a teaching or suggestion relating to ***the differential role of B7-1 and B7-2 in these pathways***.

Moreover, there is no support for the Examiner's position that since Hathcock *et al.* teach that "quantitative differences" exist in the amount of B7-1 and B7-2 expressed on activated B cells, these differences can "profoundly influence" the contribution of B7-1 and B7-2 to costimulatory function. In contrast, Hathcock *et al.* teach that "the kinetics of peak expression of these two costimulatory molecules was, in fact, ***not different***" (see page 638, first column, first full paragraph). Moreover, Hathcock *et al.* teach that "[i]***t is not yet clear whether different costimulatory molecules such as B7-1 and B7-2 mediate distinct function in the course of immune responses***" (see page 638, first column, first full paragraph) and that "[a]t the current time, ***it is not known whether B7-1 and B7-2 mediate distinct or overlapping costimulatory functions***" (see page 638, second column, first full paragraph). Thus, this reference not only fails to provide support for the Examiner's position, but further fails to provide a motivation for making the claimed invention, as Hathcock *et al.* teach that it was not known that B7-1 and B7-2 mediate different functions.

<u>B. One of ordinary skill in the art would not have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley et al.</u>

The Examiner relies on Linsley *et al.* for teaching the use of soluble B7 including fragments and derivatives to stimulate T cells. First, it is the Examiner's position that "one [of ordinary skill in the art] would have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley *et al.* because of Hathcock's teaching of B7-2 on activated B cells." Applicants respectfully submit that the proposed combination of

Hathcock et al. and Linsley et al. fails to teach or suggest the claimed invention. First, as set forth above, Hathcock et al. fails to provide the necessary ***motivation*** for the ordinarily skilled artisan to substitute soluble B7-2 for B7 in the teachings of Linsley et al. because Hathcock et al. fails to teach or suggest ***different*** roles for B7-1 and B7-2 in T cell mediated responses. Given the lack of such a teaching, the ordinarily skilled artisan would not have looked to the teachings of Linsley et al. with respect to a soluble B7-Ig fusion molecule to modulate Th2-type responses.

Moreover, Linsley *et al.* does not make up for the deficiencies of Hathcock et al. Specifically, Linsley *et al.* ***fail to distinguish between the B7-1 and the B7-2 molecules and***, thus, fails to provide the motivation for the ordinarily skilled artisan to modulate ***Th2-type responses*** by modulating B7-2 induced signals. In addition, there is no teaching or suggestion in Linsley *et al.,* as suggested by the Examiner, that such responses could be modulated by use of an agent which modulates a B7-2 induced signal. Thus, the proposed combination of Hathcock et al. and Linsley et al. as above, or with any of the other cited references, fails to teach or suggest the claimed invention and fails to provide the necessary motivation to the ordinarily skilled artisan to make the claimed invention.

C. Since Kuchroo et al. teach away from the claimed invention, they fail to make up for the deficiencies in the other cited references

The Examiner relies on Kuchroo *et al.* for teaching that "their data in experiments using anti-B7-1 and anti-B7-2 antibodies are direct evidence that interaction of the costimulatory molecules B7-1 or B7-2 with their counter receptors CD28 and CTLA-4 on T helper precursors (Thp) during antigen presentation leads to polarization of Th responses" and "that the simplest interpretation of their data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (Page 715, Column 1 and Figure 7, in particular)". Furthermore, it is the Examiner's position that Kuchroo *et al.* provide the necessary motivation to the

ordinarily skilled artisan to substitute "soluble B7-2 for B7 in the teachings of Linsley et al." because of "Kuchroo's teaching that interaction with B7-2 induces activated T cells to differentiate to become Th2 cells."

Applicants respectfully submit that Kuchroo *et al.* fail to support the above-quoted position of the Examiner. Kuchroo *et al.* teach that CD4 T helper precursor cells mature along two alternative pathways (Th-1 and Th-2) and that these pathways are differentially activated by B7-1 and B7-2. Kuchroo *et al.* focus on the implications of this biological observation, in terms of susceptibility or resistance to a particular disease, but fail to teach or suggest a method for modulating a Th2-type response in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. More importantly, Kuchroo *et al.* teach that an anti-B7-2 antibody ***enhances the production of INF*γ** (see page 708, first column, second paragraph), a cytokine known in the art and taught by Applicants to direct CD4+ T cells to differentiate into ***Th1 cells, not Th2 cells***. This cytokine is also secreted by Th1 cells. In contrast, Applicants discovered that Th2 responses can be induced by stimulation of T cells with B7-2. Thus, in view of the above described teachings of Kuchroo *et al.*, the ordinarily skilled artisan would have concluded that an agent which modulates a B7-2 induced signal in CD4+ T cells, would result in a ***Th1-type response not a Th2-type response***. In view of this conclusion, the ordinarily skilled artisan would not have been motivated to contact a population of activated CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of activated CD4+ T cells to thereby modulate a ***Th2-type response***. Given a lack of motivation to make the claimed invention in Kuchroo *et al.* or any of the cited references, the Examiner has failed to establish a *prima facie* case of obviousness and is therefore requested to reconsider and withdraw this rejection.

D. Janeway *et al.* Fail to Make up for the Deficiencies in the Primary and Secondary References

Finally, Janeway *et al.* is relied on by the Examiner, for teaching that "one of the most crucial events in the differentiation of naive CD4 T cells that respond to a ligand presented together with a costimulator is the decision whether to become a helper CD4 T cell (Th2) ... or an inflammatory CD4 T cell (Th1)" and for teaching that "if the biochemical nature of differential signaling pathways are known, pharmacological agents can be developed capable of diverting T cell responses". Janeway *et al.* is further relied on by the Examiner as providing the motivation to combine the teachings of the cited references "because signals involved in Th cell differentiation was a problem important in the art as evidenced by the teachings of ... Janeway *et al.*"

Applicants respectfully submit that Janeway *et al.* fail to make up for the above-described deficiencies of the primary and secondary references for the following reasons. First, Janeway *et al.* is a review article describing adaptive immune responses of naive lymphocytes. Although, Janeway *et al.* teach the differentiation of naive CD4 T cells into either Th2 or Th1 cells, Janeway *et al.* fail to teach or suggest a role for the B7-1 and B7-2 molecules in this differentiation process. Moreover, Janeway *et al.* fail to teach or suggest agents which modulate a B7-2 induced signal to thereby modulate a Th-2 type response in a population of CD4+ T cells. Accordingly, Janeway *et al.* fail to provide the necessary motivation to combine the teachings of the cited references as proposed by the Examiner, as Janeway *et al.* fail to teach or suggest a role for B7-2 in the differentiation of naive CD4+ T cells into either Th1 or Th2 cells.

In view of the above, Applicants respectfully submit that none of the cited references, alone or in combination, teach or suggest a method for modulating a Th2-type response in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. Moreover, in view of the above, the Examiner has failed to provide evidence that the ordinarily skilled artisan would have been motivated to

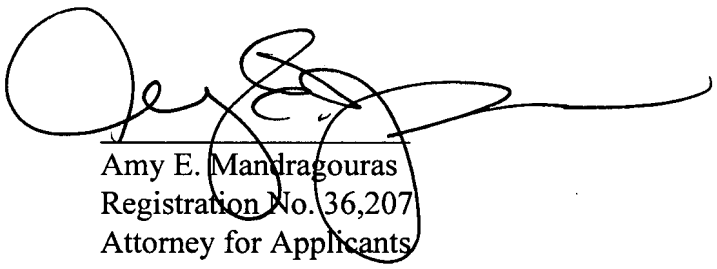
combine the teachings in the applied references in the proposed manner to arrive at the claimed invention.

For the foregoing reasons, Applicants respectfully request that the rejection of claims 1-4, under 35 U.S.C. §103, be reconsidered and withdrawn.

SUMMARY

In view of the foregoing amendments and remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



Amy E. Mandragouras
Registration No. 36,207
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

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